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DOTS-PLUS: PRELIMINARY RESULTS AND EMERGING ISSUES

Proceedings of the Meeting
of the Stop TB Working Group on DOTS-Plus for MDR-TB

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This document was written by Rajesh Gupta, Ernesto Jaramillo, and Marcos Espinal on behalf of the Stop TB Working Group on DOTS-Plus for MDR-TB.

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SUMMARY

Tuberculosis (TB) is a leading cause of adult deaths from infectious diseases. The DOTS strategy for TB control recommended by the World Health Organization (WHO) is hailed as one of the most cost-effective of all health interventions to date. In some areas, however, its success is threatened by the rise of multidrug-resistant TB (MDR-TB). To address the problem of MDR-TB, WHO in collaboration with its international partners is piloting a strategy known as DOTS-Plus. The Stop TB Working Group on DOTS-Plus for MDR-TB (convened by WHO) was created in 1999 to ensure that efforts directed towards establishing DOTS-Plus pilot projects are coordinated. Several pilot projects through the Green Light Committee (GLC), which grants access to high-quality, concessionally-priced second-line anti-TB drugs, have been established. The Working Group held its annual meeting in Tallinn, Estonia, on 10 – 12 April 2002 to discuss progress in DOTS-Plus. This document summarises the presentations, discussions, conclusions, and recommendations of the meeting.

Over 40 organizations and over 25 countries were represented by more than 150 participants at the meeting. The morning session of the first day was devoted to reviewing governance issues of the Working Group and the progress achieved by current GLC-approved DOTS-Plus pilot projects. Of the parallel sessions in the afternoon, one was devoted to convergence prospects for the GLC and the Global Drug Facility (GDF) and the other to programmatic, clinical and laboratory issues related to DOTS-Plus. The second day focused on discussions surrounding cohort definitions for the management of MDR-TB, fitness of MDR strains, best treatment strategies for MDR-TB, and next steps for the Working Group. The third day involved site visits to TB control areas in Estonia and a training session for preparing applications to the GLC.

The meeting concluded with the following recommendations:

- use MDR-TB and the GLC as tools for promoting DOTS expansion;
- continue supporting new pilot projects via the GLC;
- establish a Core Group to help manage the activities of the Working Group;
- finalize and operationalize standard cohort definitions;
- support the harmonization process of the GLC and the GDF;
- finalize a priority research agenda for DOTS-Plus;
- establish a database to catalogue MDR-TB research activities globally; and
- redistribute the terms of reference for the Working Group and its subgroups.

The next meeting of the Working Group will be held in south-east Asia in mid 2003.

BACKGROUND

Two global surveys conducted by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) published in 1997 and 2000 found multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, in nearly every country. These surveys found that the prevalence of MDR-TB is disproportionately high in some settings. In 1999, the WHO Working Group on DOTS-Plus for MDR-TB (later renamed the Stop TB Working Group on DOTS-Plus for MDR-TB) was established to advise WHO in developing policy recommendations for Member States regarding the management of MDR-TB. Four subgroups were created under the Working Group, whose duties are modified as needed:

- the Green Light Committee (GLC) to foster access to and rational use of concessionally priced second-line anti-TB drugs;
- a Subgroup on Drug Procurement Issues to address issues related to increasing access to second-line anti-TB drugs;
- a Scientific Panel on clinical, laboratory and programmatic issues to offer guidance on such issues to the GLC; and
- a Subgroup on Laboratory Issues to standardize drug-susceptibility testing (DST) methods to second-line anti-TB drugs.

On 10 – 12 April 2002, WHO and the National TB Programme (NTP) of Estonia hosted the third meeting of the Working Group to review progress thus far, and to discuss new directions for the future.

AIMS OF THE MEETING

The meeting was structured to achieve the following objectives:

1. to present the current progress of GLC approved DOTS-Plus pilot projects;
2. to discuss the harmonization of the GLC and the Global Drug Facility (GDF);
3. to discuss clinical, programmatic, and laboratory issues related to DOTS-Plus;
4. to discuss research issues related to DOTS-Plus;
5. to perform site visits to the TB control service of Estonia; and
6. to conduct a training session in developing applications to the GLC.

OPENING REMARKS

Dr Kai Vink (NTP Manager of Estonia) opened the meeting by welcoming participants to Estonia and introducing a video documentary depicting the TB epidemic in Eastern Europe during the late 1990s. The video, produced by WHO, focused on cases of MDR-TB that had already emerged. Following the video presentation was Dr Ani Aaviksoo (Ministry of Social Affairs of Estonia), who expressed how international support from the GLC and the Nordic countries was very important to Estonia. Dr Aaviksoo highlighted the link between poverty and TB, and indicated that striving for equity in health is only possible if basic issues such as improving education and alleviating poverty are also addressed. Dr Mario Raviglione (Coordinator, WHO) delivered a welcoming address on behalf of WHO, and conveyed how the activities of the Working Group relate to the activities of the Stop TB Partnership as a whole, how DOTS-Plus is integrated into the DOTS expansion movement, and how DOTS-Plus in Estonia is an example of effective international cooperation. Dr Richard Zaleskis (TB Regional Advisor, WHO-European Region) explained the situation of TB control in Eastern Europe, emphasizing that DOTS Expansion in Eastern Europe involves a joint vision including examination of the financial, clinical, epidemiological, and social issues related to TB. Dr Jim Kim (Harvard Medical School; Chair, Working Group) outlined an expanded vision of DOTS that encompasses MDR-TB and TB-HIV. Dr Kim concluded the session by stressing the importance of using DOTS-Plus, MDR-TB, and the GLC as tools to promote DOTS expansion. He highlighted examples of two countries (Estonia and Peru) where continued commitment to DOTS expansion and sustaining the NTPs resulted from the activities of the GLC.

GOVERNANCE ISSUES

From Lima to Tallinn: Progress and Governance Issues

Dr Jim Kim reported on the progress of the Working Group since the January 2001 meeting in Lima, Peru. Five new projects had been approved by the GLC, seven monitoring missions had taken place, and four pre-application assessment missions were completed. Thanks to efforts by Médecins Sans Frontières, Harvard Medical School, and WHO, the cost of second-line anti-TB drugs had fallen by up to 99%. Eli Lilly and Company had agreed to continue their support of DOTS-Plus by extending their concessional pricing agreement and doubling the quantities of drugs provided. A long-term procurement arrangement between the International Dispensary Association and WHO was finalized. Future activities for the Working Group include establishing more pilot projects, expanding the role of the laboratory to support MDR diagnosis, optimizing GLC operations, facilitating technology transfer of drugs, conducting economic analyses of pilot projects, increasing research activities according to a prioritized research agenda, and promoting advocacy of a comprehensive TB control strategy. Lastly, the concept of a Core Group was proposed. This Core Group would improve the efficiency of the Working Group by overseeing the activities of the Working Group, liasing between the various parties (Working Group members, Secretariat, and other Stop TB Working Groups), and the Secretariat of the Working Group.

PROGRESS IN DOTS-PLUS PILOT PROJECTS

DOTS-Plus in Estonia

Dr Kai Vink presented DOTS-Plus in the context of the TB epidemic in Estonia. The NTP was established in 1998 and country-wide coverage with DOTS was achieved in May 2000. Case notification has steadily increased since 1990, with decreases occurring in 1999 (potentially attributable to change in notification due to DOTS) and 2001 (representing an actual decrease in TB incidence). In 2001, MDR-TB levels were 14.2% in new and 42.1% in previously treated cases. DOTS-Plus officially started in August 2001, although Estonia has managed its MDR-TB patients since 1996. Nearly 80% of patients are resistant to greater than five drugs in the "DOTS-Plus" cohort of 80 patients. Since GLC approval, 103 patients have been enrolled on treatment. Treatment is individualized, and current conversion rate at six months is 61%. High levels of alcoholism in MDR-TB patients is one of the main problems faced by the NTP.

DOTS-Plus in Latvia

Dr Vaira Leimane (NTP Latvia) presented the MDR-TB situation in Latvia. From 1997 – 2001, the levels of primary and acquired MDR-TB have remained high but fairly stable, at 9 – 10% and 29 – 35%, respectively. Cumulative data from Latvia indicates that 348 (44%) patients are on treatment, 181 (23%) were cured, 101 (12.5%) died, 64 (8%) were lost from follow-up, and 101 (12.5%) are under symptomatic treatment. Of the new MDR-TB cases diagnosed in 2001, 6% were co-infected with HIV, and there was an average of three to four risk factors per patient. In 2001, a new and more aggressive treatment strategy was implemented. A full cohort evaluation from 1999 showed that 64% of patients were cured, 24% failed treatment (of which 30% died), 3% died, and 9% defaulted (of which 23% were recovered and began new treatment). Of note is that only two patients (1.3%) relapsed after being declared "cured" (one year follow-up data). Interim outcomes from the 2001 cohort show that 67% of patients are likely cures, 8% are defaulters, 9% are failures, 3% died, and 13% did not yet convert. Delays in the flow of funds for the purchase of second-line anti-TB drugs is the main difficulty faced by the NTP.

DOTS-Plus in Tomsk

Dr Gennady Peremetin (Tomsk Oblast TB Dispensary) described the DOTS-Plus pilot project in Tomsk Oblast, Russian Federation. From 1994 – 1999, DOTS was implemented in the prison and civilian sectors of Tomsk. In late 2000, DOTS-Plus was implemented in the prison sector and, subsequently, in the civilian sector in early 2001. Since 1996, TB incidence has remained fairly stable at 107.7 – 117.6 per 100,000. In 2001, MDR-TB among new cases in the civilian and prison sectors was 10.2% and 15.6%, respectively. To date, 177 patients are enrolled of which 160 (90.4%) are still on treatment. Culture conversion rate is 71% for patients on treatment. Patient motivation is a strong component of this programme and includes incorporation of social workers into TB services, consultation of inmates being released, procurement of clothes, identifying contact relatives in the civilian sector, nutritional support, and payment of transportation expenses. Current constraints include lack of drug supply due to the limited number of suppliers registered in the Russian Federation.

DOTS-Plus in Manila

Dr Thelma Tupasi (Tropical Disease Foundation/Makati Medical Center) presented the DOTS-Plus pilot project in Manila, Philippines. The project is a collaboration between the public and private sectors in Manila. Although management of MDR-TB patients began in April 1999, the accrual of the majority of patients did not occur until the project was approved by the GLC in October 2000. Most MDR-TB patients (84.2%) are referred from the private sector. For data available on 100 MDR-TB patients, 70 (70%) are resistant to four or five first-line anti-TB drugs. In addition, resistance to ciprofloxacin among MDR-TB patients has increased from 10.3% in 1989 – 1994 to 51.4% in 1995 – 2000. In the same patients, resistance to ofloxacin increased from 24.0% to 51.4%. Under programmatic conditions, treatment outcome data for 117 patients are as follows: approximately 70% of patients are cures or likely cures, 9% failed treatment or are likely failures, 9% defaulted, 2% transferred out, and 11% died. Severe adverse drug reactions were reported in 8.7% of patients. Overall problems include lack of consistent funding for the programme, lack of standard drug resistance surveillance (DRS) data in the Philippines, and the need for increased incorporation of the private sector into the DOTS programme.

DOTS-Plus in Lima

Dr Jaime Bayona (Socios en Salud) described the DOTS-Plus project in Lima, Peru. Established in 1996, the project uses individualized treatment regimens for patients failing the standard MDR-TB treatment regimen provided by the NTP in Peru. As of 2001, the project also places select Category I treatment failures (i.e. those from Lima) directly onto individualized regimens. Data from 154 patients revealed that 79% were cured, 12% failed, 8% died, 1% transferred out, and zero defaulted. In Category I failures, the standard Category II re-treatment regimen yielded only a 40% cure rate in this setting. However, for defaulters and relapses of Category I, cure rates were 74% and 80%, respectively. Cohort analysis of the standard MDR-TB treatment regimen showed that 46.7% of patients were cured, 33.7% failed treatment, 13.4% abandoned treatment, and 16.4% died. The main challenge for the project is further expansion in Peru.

Feasibility and Cost-effectiveness of DOTS-Plus in Peru

Drs Marcos Espinal (WHO) and Katherine Floyd (WHO) presented an evaluation of the feasibility and cost-effectiveness of the DOTS-plus programme in Peru. This evaluation was undertaken for the cohort of 466 patients enrolled between the start of the programme in October 1997 and March 1999, who were treated with a standardized 18-month regimen. Overall, 225 (48%) patients were cured, 57 (12%) died, 131 (28%) failed, and 53 (11%) defaulted. Almost 90% of patients complied with treatment. Among MDR patients, resistance to five or more drugs was significantly associated with poor treatment outcome (death, failure, default). Among patients who were declared cured, 96% had a negative smear after six months of treatment and 86% had a negative culture after six months of treatment. The total annual cost of the programme was about US$ 0.6 million per year, equivalent to 8% of the NTP budget. The cost per patient treated was US$ 2381. The cost per disability-adjusted life-year (DALY) gained was US$ 211, and US$ 165 at drug prices projected (at the time of analysis) for 2002.

Further analysis was also presented for two other treatment strategies, using data for the existing standardized programme and data from the published literature. These strategies

were: 1) implementation of the existing standardized programme, plus individualized treatment for those who failed the standardized drug regimen, and 2) implementation of the existing standardized programme, plus individualized treatment for failures of the standardized programme, and in addition enrolment in the standardized programme of Category I failures found to have MDR (i.e. the re-treatment regimen is bypassed for Category I failures with MDR). Results showed that the use of these strategies would increase effectiveness in terms of both the cure rate and DALYs gained, with total annual costs ranging from US$ 0.7 to 0.9 million (8-12% of the NTP budget) in an optimistic cost scenario (individualised treatment cost per patient of US$ 2500) and US$ 1.2 – 2.0 million (25-34% of the NTP budget) in a high-cost scenario (individualised treatment cost per patient of US$ 10,000). The cost per DALY gained would range from a mean of around US$ 200 in the optimistic cost scenario to US$ 300-400 (depending on the strategy) in the high-cost scenario.

The main conclusions of the study were:

- Delivery of second-line anti-TB drugs under programme conditions is feasible, provided a strong TB control programme is already in place.
- It is important to make efforts to increase cure rates – for example by using stronger drugs and individualised treatment for some patients.
- All three strategies assessed are cost-effective in middle-income countries when compared with standard benchmarks.[*]

GREEN LIGHT COMMITTEE AND GLOBAL DRUG FACILITY: PROSPECTS FOR CONVERGENCE

Quality Assurance for the Procurement of Anti-TB Drugs

Dr Souly Phanouvong (WHO) presented quality assurance issues related to anti-TB drugs. Quality assurance is needed especially for anti-TB drugs as low-quality drugs can lead to discrediting of the NTP and to the emergence of MDR-TB. In a survey performed by WHO, only 7% of drugs (for several diseases, including TB) contained the correct ingredients. Quality assurance has technical and regulatory elements nested in a legal framework for each country. Three practical approaches were presented: ensuring only drugs that meet set standards for quality are purchased, verifying that shipped goods meet specifications, and monitoring and maintaining the quality of the drugs purchased.

Green Light Committee (GLC): From Theory to Reality

As Chair of the GLC, Dr Kitty Lambregts-van Weezenbeek [Royal Netherlands Tuberculosis Association (KNCV)] presented the history, current activities, and future prospects of the GLC. DOTS-Plus is programmatically more complicated than DOTS and there are several obstacles to its implementation. Accordingly, implementation of DOTS-Plus needs to proceed in a rational manner. At the same time access to second-line anti-TB drugs is currently increasing as a result of activities of the Working Group. The GLC was established to ensure that projects receiving these drugs were in line with the *Guidelines for*

[*] Full details of this study can be found in Suarez PG, Floyd K, Portocarrero J, *et al*. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002. **359**: 1980-1989.

Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB. In addition, the GLC performs continuous monitoring of these projects, coordinates and facilitates technical assistance to potential projects, and, ultimately, participates in the policy development process for MDR-TB. Outcomes of the process include approval of eight projects for a total of 2370 patients and promotion DOTS expansion. Future issues include linking and harmonizing with the Global Drug Facility and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), increasing DRS activities globally, and monitoring the effect of further reductions in prices and increases in suppliers of second-line anti-TB drugs.

Global Drug Facility (GDF): Improving Access to First-Line Anti-TB Drugs

Dr Jacob Kumaresan (Executive Secretary, Stop TB Partnership), presented the activities of the GDF. The GDF is managed by the Stop TB Partnership secretariat and is a novel approach to securing access to high-quality first-line anti-TB drugs. The GDF is currently focusing on standardizing products. GDF operations involve an application and review process, country visits, drug procurement, and monitoring. Through the GDF, first-line anti-TB drug costs have been reduced by up to 30%. Applications are approved for 17 countries, with drugs being secured for 643,013 patients.

Harmonization of the Global Drug Facility and the Green Light Committee

Ms Gini Arnold (WHO) and Mr Rajesh Gupta (WHO) presented a potential plan of harmonization of the GDF and the GLC. Harmonization was discussed in the context of six topics: scope, governance, procurement, administration, applications and review, and financing. While the scope of the two projects are different (with the GLC more focused on policy development), it is possible for the GDF, via the GLC process, to include second-line anti-TB drugs within its mandate. In terms of governance, accountability may need to remain separate for legal reasons, but both processes could provide reports to all relevant institutions in order to increase transparency. The review processes could be streamlined via a joint application form, standard review cycle, having observers from each process attend the meetings of the other, and combining monitoring missions. Funding could be channelled to cover all activities of both processes and to provide grants for second-line anti-TB drugs, but should be done so under a clear and transparent process. While some risks exist (such as dilution of identity of each process and potential choices in priority setting), harmonization appears to be beneficial to both.

Participants supported the notion of convergence and suggested that the respective secretariats develop details of the harmonization plan based upon the presentations. It was emphasized that harmonization should occur in a manner and with a product that is advantageous to both processes. Quality of drugs provided by the GLC and GDF should not suffer, and should be guaranteed via a process similar to the scheme used to prequalify suppliers of anti-retrovirals. Further discussion of the harmonisation plan indicated the need for linking the GDF and GLC to the GFATM. Participants expressed concern that if the Global Fund were to finance projects without GLC review, procurement of drugs outside the scope of the GLC may disrupt the market for second-line anti-TB drugs and costs of treatment regimens would increase. In addition, such projects would not be monitored and may contribute to resistance to second-line anti-TB drugs.

PROGRAMMATIC, CLINICAL, AND LABORATORY ISSUES

Defaulting Treatment and Side-effects: Obstacles to Managing Patients?

Dr Manfred Danilovits (NTP Estonia) opened the presentation with cohort data from 1999 for 112 MDR-TB cases: 57% treatment success, 21% defaulters, 6% failures, and 16% deaths. For drug-susceptible TB patients, the rate of treatment success and default in 1999 was 74.9% and 10.0%, respectively. In 2000, the rate of treatment success and default improved to 83.1% and 7.7%, respectively. High default rates in Estonia are primarily attributed to alcohol abuse and prior imprisonment. Socioeconomic and health education problems, drug abuse, and co-infection with HIV are also contributing to default. The introduction of several administrative measures, a case management team, enablers and incentives, psychological support, and overall good communication (all specifically tailored for the high-risk defaulter populations) are key to improving adherence. Although a specific management algorithm exists for management of adverse reactions, most patients present with only mild symptoms and can be managed without alteration in therapy. Dose reduction or drug elimination are last options for management of adverse reactions.

Adherence to Treatment: Role of Social Support

Dr Ernesto Jaramillo (WHO) began the presentation by indicating that adherence to treatment is one of the biggest challenges facing both TB patients and the NTP. It is commonly accepted by many health care workers that poor adherence to treatment is mainly a problem arising from misconceptions of the patient about the disease and its treatment. Health education is therefore usually seen as the most powerful tool to overcome defaulting in treatment. However, human behaviour is complex and there is no single psychosocial construct for health behaviour that is reliable and accurate in predicting treatment adherence, including TB. Human social behaviour is the result of factors under the control of the individual (agency) as well as forces that are mostly beyond its control (structure). There is increasing evidence that default rates decrease once the structural forces impinging on adherence to TB treatment are improved (by the provision of social support). Social support can be delivered to TB patients in various ways: top-down versus bottom-up approaches; tailored versus generic interventions; community-based versus donor-driven packages; and interventions targeting patients as subjects of their own social development. There is still a lack of research on the efficacy and feasibility of these different approaches in the context of low-income countries.

Role of Training in DOTS-Plus

Mrs Karin Bergstrom (WHO) described the role of training in the implementation of DOTS-Plus. In-service training enhances the competence of the health care providers and managers in implementing the case strategy. Competence can be ensured via a systematic approach to training management, clear definitions of tasks, assignment of responsibilities, competency-based training programmes, and a systematic evaluation of competencies at the end of training. Constraints to maintaining compliance include the stringent requirements for training versus the low case-load (relative to drug-susceptible TB), and the additional components of training needed for DOTS-Plus. However, since competence does not necessarily guarantee performance, in-service training does not ensure that health care workers perform according to standards. In addition, pilot projects are often well-funded and may not represent the conditions appropriate for large-scale implementation.

Surveillance and Laboratory Issues

1. Drug Resistance in Eastern Europe: Do We Know the Magnitude of the Problem?

Dr Mohammed Aziz (WHO) presented the progress of DRS in Eastern Europe. The WHO/IUATLD global project on DRS began in 1994 with reports published in 1997, 2000, and 2003 (projected). Data for DRS is only available from 18% of Eastern and Central European countries. However, in these areas, the average level of MDR-TB and rifampicin-mono resistance is 2.5% and 5%, respectively. DRS should be a prerequisite for implementation of DOTS-Plus, and priority should be placed on expanding DRS activities in Central and Eastern Europe.

2. Role of the Laboratory in the DOTS-Plus Strategy

Dr Leonid Heifets (National Jewish Medical Research Center) described the dilemmas and options in identifying patients with drug-resistant TB. Two options were presented: to test the subset of patients that did not respond to the initial treatment or to test all new patients. Each option has its own advantages and disadvantages. In order for rapid turnaround time for laboratory reports to occur, a centralised laboratory system is needed with the following requirements: ability to process large volumes of specimens, equipped with biosafety requirements, use of agar medium for culture isolation and DST, and capability for direct DST (to at least isoniazid and rifampicin) on agar plates. The Ural model in Sverdlovsk is based on a centralized laboratory performing DST to all new patients. The return time for reports is as follows: smear - within 24 hours; 70% of culture results - within three weeks; DST (direct) - three to four weeks; DST (indirect) – six weeks; and confirmation of *Mycobacterium tuberculosis* – three weeks.

3. Standardization and Quality Control to Improve Reliability of Drug-susceptibility Testing

Dr Sven Hoffner (Swedish Institute for Infectious Disease Control) explained the problems with current DST methods. Three general types of DST are possible: solid medium [proportion method (reference technique), absolute concentration method (reference technique), and resistance ratio method (reference technique)], broth medium [Bactec 460 (reference technique), MGIT (alternative techniques), and BacT/ALERT (alternative technique)], and molecular methods [Line Probe Assay (LiPA), DNA Chip Technology, and Pyrosequencing]. The disadvantages include unreliable results with standardization and quality assurance, slow processes (especially for methods based on solid medium), need for laboratory safety, cost (especially for more rapid methods), and need for expert knowledge (especially for molecular techniques). Quality assurance is currently performed by the WHO/IUATLD Supranational TB Laboratory Network, which has improved the sensitivity and efficiency of its member laboratories. Standardization of methods, however, is still needed.

UNFINISHED BUSINESS

Cohort Analysis: The Need for Standards

Dr Peter Cegielski [Centers for Disease Control and Prevention (CDC)] presented standard cohort definitions and a core data set of monitoring variables, which were developed in close collaboration with Latvian State Center for TB and Lung Disease, Medical Research Council of South Africa, Partners In Health, and WHO. The goal of the process was to develop definitions by using standard DOTS cohort definitions and monitoring variables as a template, and modifying those definitions to fit MDR-TB management as needed. Cohort definitions included case registration and outcome definitions. The core data set contained demographic data and social history, medical history, current TB information, follow-up information, and interim and final outcomes (as defined). The document will be distributed for comments to members of the Working Group, and finalized accordingly. It will be recommended that all DOTS-Plus pilot projects adhere to these definitions to ensure that data can be compared across projects.

Fitness of MDR-TB: Superbug or Not?

Dr Marcos Burgos (Stanford University) began this session by explaining fitness can be inferred from four different type of studies: laboratory data, epidemiological and clinical studies, molecular epidemiology, and surveillance and modelling data. Previous data with different approaches from six studies indicated drug-resistant strains were from 0.16 to 3.00 times as fit as drug-susceptible strains. In San Francisco, data of ten years collected from a prospective molecular epidemiological study showed that isoniazid-resistant strains were 0.2 as fit as drug susceptible strains. Rifampicin-resistant strains were nearly three times as fit as drug-susceptible strains, but in 80% of the cases studied these strains were obtained from patients that were also HIV seropositive. No transmission of MDR-TB resulting in active cases of TB was observed. It was concluded that in San Francisco isoniazid-resistant strains and MDR-TB appeared to be less fit than drug-susceptible strains, but that this fitness may be offset by a decreased host response (i.e. HIV) and longer period of infectiousness.

Dr Megan Murray (Harvard School of Public Health) followed by examining the relative strengths and weaknesses of different methodologies in measuring fitness. Laboratory studies have indicated that resistance can impose biological costs, but that subsequent mutations may compensate for the original loss in fitness. Cluster studies demonstrate that MDR-TB is between 0.09 and 7.84 times as fit as drug-susceptible TB, but cluster studies may not be accurate because of detection bias, confounding, and infection dynamics. Epidemiological studies indicate that drug-resistant TB is equally as fit as drug-susceptible TB, but only a few studies have been conducted using this methodology. Model-based estimates rely on average estimates and make several assumptions; however, since drug-resistant strains seem not to be homogeneous, the appropriateness of using estimates based on averages is questionable. Overall, the data appear to very heterogeneous, indicating that setting-specific analyses may be best given the setting-specific epidemiology of MDR-TB.

Best Treatment Strategies for Settings of High MDR-TB

Dr Michael Kimerling (University of Alabama at Birmingham) presented a decision analysis to determine the impact of DOTS in a confined setting (Colony 33 prison setting

from the Russian Federation) with a high background rate of drug resistance. Three strategies for Category I failures were analysed: use of standard short-course chemotherapy (Category II), use of an empiric MDR treatment regimen, and use of an empiric MDR treatment regimen based upon risk stratification of patients. The analysis revealed that the empiric MDR strategy and the risk stratification strategy decreased the amplification of MDR-TB. With a 70% reduction in MDR-TB drug costs, the risk stratification strategy was less expensive and more effective than standardized short-course chemotherapy for this population. With a 90% reduction in MDR-TB drug costs, the risk stratification strategy and empiric MDR strategy were less expensive and more effective than standardized short-course chemotherapy for this population. Of note is that the model is conservative, static, and may not be applicable for conditions outside those for which it was created, and that several items were not addressed in the analysis.

Prioritized Research Agenda for MDR-TB

Dr Alan Hinman (Task Force for Child Survival and Development) presented a prioritized research agenda based upon the 14 research areas identified at the last meeting of the Working Group in Lima in January 2001. The proposed priority topics are as follows:

- define optimal standardised protocols to treat MDR-TB,
- identify threshold indicators for implementing DOTS-Plus,
- ascertain programmatic, laboratory, and resource requirements for DOTS-Plus,
- quantify the risk of MDR-TB in various populations,
- establish optimal timing for laboratory testing,
- assess programmatic utility of rapid diagnostics tests, and
- create standards and parameters for testing of second-line anti-TB drugs.

In addition, other non-research priority activities were presented. These activities are as follows:

- implement and operationalize cohort definitions,
- implement and operationalize core data set for programme evaluation,
- carry out surveillance for adverse events,
- evaluate MDR-TB training activities, and
- initiate and evaluate infection control procedures.

To ensure that research activities were prioritised appropriately, WHO would distribute a questionnaire to all Working Group members to rank the list of research topics presented. Based on the results of the questionnaire, a final priority research agenda would be created. In addition, WHO would begin the process of cataloguing all MDR-TB related research activities to ensure that the items listed in the priority research agenda were being addressed.

TRAINING SESSION FOR APPLYING TO THE GREEN LIGHT COMMITTEE

A workshop to introduce the process for applying to the GLC led by Dr Ernesto Jaramillo and Dr Kitty Lambregts was held after the meeting of the Working Group in Tallinn. The workshop was facilitated by the GLC Secretariat (WHO) and attended by 15 participants of

the Working Group meeting from Costa Rica, India, Kazakhstan, Malawi, Mexico, Russian Federation, and South Africa. Participants were briefed on the antecedents of the DOTS-Plus strategy, and the history and *modus operandi* of the GLC. The references *Instructions for Applying to the Green Light Committee* and *Guidelines for Establishing DOTS Plus Pilot projects for the Management of Multidrug-resistant Tuberculosis (MDR-TB)* were distributed, and a review of the main components of each document was made. The facilitator addressed questions raised by participants, and technical assistance in application development was offered to those countries interested in implementing a DOTS-Plus pilot project.

SITE VISIT

Visits to the prisons, MDR-TB hospital, and other health facilities were conducted to observe the implementation of DOTS and DOTS-Plus. Participants were impressed with the quality of the Estonian NTP, the rapid implementation and scaling up of DOTS and DOTS-Plus in the area, and the cooperation built with several international partners.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, participants re-emphasised that implementation of the DOTS strategy prevents the emergence of MDR-TB, and that priority should therefore be placed on DOTS implementation. However, as part of DOTS expansion activities, some countries need to consider now the implementation of DOTS-Plus to address their MDR-TB burden.

In addition, the following recommendations emerged from the meeting:

1) MDR-TB and the GLC should be used as a tool to promote DOTS expansion.

2) The prioritized research agenda should be distributed to the Working Group for comments and finalized as soon as possible.

3) WHO should implement its plan to catalogue all research activities related to MDR-TB into a research database to be made available to all Working Group members.

4) Cohort definitions and core data set should be distributed to the Working Group for comments, finalized, and operationalized as soon as possible.

5) Pilot projects reviewed by the GLC should continue to be implemented and supported by the international community.

6) Advocacy related to DOTS-Plus activities should be increased.

7) Activities related to access to drugs should be maintained, the drug procurement process should continue to be monitored, and ensuring quality of drugs provided by the GLC and GDF should remain a priority activity for WHO.

8) A plan for harmonization of the GLC and the GDF should be jointly drafted by the secretariats of each and submitted to the Stop TB Coordinating Board.

9) A Core Group should be established to help facilitate the activities of the Working Group and should begin its work as soon as possible.

10) Technology transfer of second-line anti-TB drug production is widely supported and should be facilitated by the Working Group as needed.

The meeting concluded with the formal appointment of selected members of the Working Group to the Core Group. The next meeting of the Working Group will be held in mid-2003 in south-east Asia.

ANNEX 1: AGENDA FOR MEETING OF THE STOP TB WORKING GROUP ON DOTS-PLUS FOR MDR-TB

Day 1	**Opening Remarks**	
8:30 AM – 8:35 AM	Video	
8.35 AM – 9.00 AM	Dr Siiri Oviir Minister of Social Affairs of Estonia	
	Dr Mario Raviglione Stop TB Department, WHO	
	Dr Richard Zaleskis, WHO European Region	
	Dr Jim Kim Chairman of the Working Group	
Chairperson: R. Zaleskis	*Rapporteur: Marcos Burgos*	
	Session 1: Governance Issues	
9:00 AM – 9:15 AM	Governance of the Working Group Proposal for a Core Team	J. Kim
9:15 AM – 9:45 AM	Discussion and Recommendations	
	Session 2: DOTS-Plus Progress	
9:45 AM – 10:00 AM	DOTS-Plus in Estonia	K. Vink
10:00 AM – 10:15 AM	DOTS-Plus in Latvia	V. Leimane
10:15 AM – 10:30 AM	DOTS-Plus in Tomsk	G. Peremitin
10:30 AM – 11:00 AM	Discussion	
11:00 AM – 11:30 AM	Coffee Break	
11:30 AM – 11:45 AM	DOTS-Plus in Manila	T. Tupasi
11:45 AM – 12:00 M	DOTS-Plus in Lima	J. Bayona
12:00 M – 12:30 PM	Lessons Learned	Panellists

12:30 PM – 12:50 PM	Special Presentation Feasibility and Cost-effectiveness of DOTS-Plus in Peru	M. Espinal K. Floyd
12:50 PM – 1:10 PM	Discussion	
1:10 PM – 2:30 PM	Lunch – Restaurant Seasons at the Radisson	

Session 3: Parallel Sessions

	GLC and GDF **Prospects for Convergence**	**Room Hansa**
Chairperson: Tim Healing	*Rapporteur: M. Henkens*	
2:30 PM – 2:45 PM	Quality Assurance in the Procurement of Anti-tuberculosis Drugs	S. Phanouvong
2.45 PM – 3.00 PM	Green Light Committee: From Theory to Reality	K. Lambregts
3:00 PM – 3:15 PM	Global Drug Facility: Improving Access to First-line Anti-tuberculosis Drugs	J. Kumaresan
3:15 PM – 3:30 PM	GLC/GDF Points of Convergence	R. Gupta V. Arnold
3:30 PM – 4:00 PM	Discussion	
4:00 PM – 4:30 PM	Coffee Break	
4:30 PM – 5:30 PM	Discussion and Recommendations to Stop TB Coordinating Board	
	Programmatic, Clinical and Laboratory issues	**Room Cuxhaven**
Chairperson: Thelma Tupasi	*Rapporteur: Bertie Squire*	
2:30 PM – 2:45 PM	Role of Surgery in the Management of MDR-TB	M. Perelman
2:45 PM – 3:00 PM	Defaulting Treatment and Side-effects: Obstacle to Managing Patients?	M. Danilovits

3:00 PM – 3:15 PM	Adherence to Treatment: Role of Social Support	E. Jaramillo
3:15 PM – 3:30 PM	Role of Training in DOTS-Plus	K. Bergstrom
3:30 PM – 4:30 PM	Discussion	
4:30 PM – 5:00 PM	Coffee Break	
5:00 PM – 5:30 PM	Surveillance and Laboratory Issues (10 min each)	
	Drug Resistance in Eastern Europe: Do We Know the Magnitude of the Problem?	M. Aziz
	Role of the Laboratory in the DOTS-Plus Strategy	L. Heifets
	Standardisation and Quality Control to Improve Reliability of DST	S. Hoffner
5:30 PM – 6:00 PM	Discussion	
8:00 PM	Reception at Tallinn Town Hall	

Day 2	**Session 4: Unfinished Business**	
Chairperson: Pierre Chaulet		*Rapporteur: Joia Mukherjee*
8:30 AM – 8:45 AM	Cohort Analysis: The Need for Standards	P. Cegielski
8:45 AM – 9:30 AM	Discussion and Recommendations	
9:30 AM – 10:00 AM	Roundtable	(10 min each)
	Fitness of MDR-TB: "Superbug" or Not?	M. Murray M. Burgos C. Dye
10:00 AM – 11:00 AM	Discussion	
11:00 AM – 11:30 AM	Coffee Break	
11:30 AM – 11: 45 AM	Best Treatment Strategies for Settings of High MDR-TB	M. Kimerling

11:45 AM – 12:00 PM	Prioritised Research Agenda	A. Hinman
12:00 PM – 1:00 PM	Discussion	
1:00 PM – 2:30 PM	Lunch – Restaurant Seasons at the Radisson	

Session 5: Next Steps

Chairperson: Alan Hinman *Rapporteur: M. Grzemska*

2:30 PM – 4:00 PM	Report of the Rapporteurs	
4:00 PM – 4:30 PM	Coffee Break	
4:30 PM – 5:30 PM	Administrative Issues of the WG: Structure, Next Meeting, Next Steps	All
5:30 PM – 5:40 PM	Closing Remarks	M. Espinal
8:00 PM	Festive Dinner at Lillepaviljon	

Day 3	**Site Visits and Training Session**
AM	Site Visit of MDR-TB Management Programme in Estonia: Tallinn and Tartu. Transportation, snack bags and lunch will be provided
PM	Training Session on Applying to the GLC

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ANNEX 3: TERMS OF REFERENCE FOR THE STOP TB WORKING GROUP ON DOTS-PLUS FOR MDR-TB

"DOTS-Plus for Multidrug-Resistant Tuberculosis"

A Stop TB Working Group Convened by WHO

Terms of Reference

The Working Group on "DOTS-Plus for MDR-TB" is an inter-institutional arrangement of many partners involved in the management of multidrug-resistant tuberculosis (MDR-TB) under the umbrella of Stop TB convened by WHO.

Rationale for the Working Group

The WHO/IUATLD Global Project on Drug Resistance Surveillance (DRS) has shown that MDR-TB is present in almost all countries surveyed and that a few "hot spots" with very high MDR-TB prevalence exist. The potential spread of MDR-TB could be a threat to the success of DOTS, the WHO strategy for TB control. DOTS is a five-component policy package acknowledged by the World Bank as one of the most cost-effective interventions in human health.

Following identification of such "hot spots," there was an increasing call for action to prevent and contain the spread of MDR-TB. After publication of the Global Report on DRS in 1997, WHO initiated a series of consultations to design a strategy to address MDR-TB as a potential public health problem. In April 1998, WHO and Harvard/PIH co-sponsored a meeting in Cambridge, USA, to discuss a potential approach to address MDR-TB in developing countries. Later in July 1998, a second meeting at WHO headquarters in Geneva, Switzerland, brought together recognized worldwide technical experts to produce two generic protocols for the management of MDR-TB.

In January 1999, a third meeting took place at WHO headquarters to define a strategy targeting MDR-TB. The main recommendations were to establish a Working Group on DOTS-Plus for MDR-TB, to focus on drug access, to negotiate with the pharmaceutical industry for a reduction in drug prices, and to elaborate guidelines for implementation of pilot projects and for drug susceptibility testing of second-line anti-TB drugs.

In industrialized countries, management of MDR-TB is based on the use of tailored treatment regimens with second-line anti-TB drugs according to the patient's drug susceptibility pattern. However, no conclusive evidence at programme level is yet available on how feasible this

approach to designing regimens would be in low- and middle-income countries. In some of these settings, drug-susceptibility testing (DST) is not widely available and second-line anti-TB drugs are not affordable. Potential management strategies for MDR-TB must therefore be adapted and carefully tested before recommendations are issued.

A Working Group was created in 1999 by WHO to assess the feasibility and cost-effectiveness of management strategies for MDR-TB, and to generate evidence-based policy on the management of MDR-TB in middle- and low-income countries. Several pilot projects have been established. The results of these pilot projects will generate sufficient data for WHO eventually to develop international policy recommendations. With the establishment of the Stop TB structure, the Working Group became the Stop TB Working Group on DOTS-Plus for MDR-TB.

Objectives of the Working Group

In order to address MDR-TB care and control comprehensively, efforts will be coordinated, and collaborative work in partnership with other institutions of recognized experience and prestige promoted. The objectives of the Working Group are as follows:

1. To assist in producing policy recommendations for Member States on the management of MDR-TB, based on the assessment of the feasibility, effectiveness, and cost-effectiveness data generated by pilot projects implemented by the agencies and institutions participating in the Working Group, or by WHO;

2. To coordinate and monitor the implementation of internationally comparable pilot projects for the management of MDR-TB. In most cases, the representatives of participating agencies and institutions will be acting as principal investigators on behalf of the agency and institution they represent;

3. To establish a system that allows WHO Member States to have access to high-quality second-line anti-TB drugs at reduced prices and, at the same time, prevent misuse of such drugs;

4. To review progress achieved within the DOTS-PLUS initiative; and

5. To identify resources to fund and implement DOTS-PLUS pilot projects and to assist with global coordination of the initiative.

Membership

Participation in the Working Group is open to any institution or technical expert (not affiliated with any institution) serving in a personal capacity and willing to help achieve the goals mentioned in the above-listed terms of reference. The Working Group is composed of one representative of each participating agency/institution and technical experts in their personal capacity. Institutional representatives in the Working Group and its subgroups are designated at the discretion of the institution.

The Working Group selects a chair from among the representatives of the Partners to preside over the meetings of the Working Group. The chair of the Working Group is selected for a period of two years and represents the Working Group during meetings of the Stop TB Coordinating Board. WHO will consult the chair for advice on when to convene meetings of the Working Group. Each subgroup of the Working Group will select its chair for the duration of the subgroup's existence, and preside over the meetings of the subgroup.

WHO will provide the secretariat functions for meetings of the Working Group and its subgroups.

Progress to Date

The Working Group was established in 1999 before the creation of the Stop TB structure. Therefore, work began and is now underway to address the above objectives. In 2002, a Core Group was established to assist the Secretariat in rapidly implementing the recommendations of the Working Group and in pursuing its objectives and aims. Accordingly, the Core Group has the following tasks:

- To assist with the preparatory work for the (annual) Working Group meetings.
- To hold regular conferences to assist in faster decision-making related to Working Group activities.
- To oversee activities of the ad hoc or subgroups of the Working Group.
- To liaise with the Green Light Committee to assist countries in implementation of Green Light Committee recommendations as needed.
- To interact with other Stop TB Working Groups to coordinate activities.

In addition, several subgroups within the Working Group exist:

1. The Subgroup on Laboratory Issues was created to make recommendations concerning standard guidelines for DST for second-line anti-TB drugs. The resulting document *Guidelines for Drug-Susceptibility Testing to Second-line Anti-TB Drugs for DOTS-Plus* has been finalized. Although this subgroup was dissolved, it has been recreated and now focuses on setting the basis for determining standards for DST to second-line anti-TB drugs.

2. The Scientific Panel on Programmatic, Laboratory, Clinical Issues was created with two objectives:
   - To prepare and review guidelines to implement DOTS-Plus pilot projects.
   - To assess the data generated by DOTS-Plus pilot projects in order to, ultimately, advise WHO in developing policy recommendations for its Member States.

- To provide technical advice to the Green Light Committee and resolve programmatic and clinical issues (including establishing case definitions) regarding for management of MDR-TB.

The first objective of the Scientific Panel is complete. The resulting document has been finalized and is entitled *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*. However, this document will be reviewed and revised periodically to reflect the most recent data available. The second objective will be addressed as data are generated and collected. The third objective is being addressed as the Scientific Panel advises WHO on the work of the Green Light Committee.

3. The Subgroup on Drug Procurement Systems was recreated as the Subgroup on Procurement Issues. Originally, the Subgroup on Drug Procurement Systems was created to make recommendations for increasing access (primarily in terms of lowering cost) to high-quality second-line anti-TB drugs. The activities of this subgroup have resulted in a large decrease in the price of second-line anti-TB drugs, and the establishment of two procurement arrangements that (combined) will supply complete treatment courses for DOTS-Plus pilot projects which the Green Light Committee finds to be in accordance with the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*. This recreated subgroup has the following objectives:

   - To resolve registration issues of capreomycin, cycloserine, and granular PAS in the Russian Federation.

   - To identify potential partners for technology transfer of capreomycin and cycloserine.

   - To develop a strategy for increasing access to diagnostics.

   - To develop a strategy for increasing access to ancillary drugs for the management of adverse reactions.

   - To perform a second survey of the global use of second-line anti-TB drugs.

As a special body of the Working Group, the Green Light Committee (created in 2000 by the Subgroup on Drug Procurement Systems for second-line anti-TB drugs as its implementing arm and natural evolution) has the following tasks:

- To evaluate proposals from potential DOTS-Plus pilot projects to determine if those projects have adequately addressed all issues highlighted in the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB* so that such projects may benefit from concessionally-priced second-line anti-TB drugs, as a result of the work of the Subgroup on Drugs Procurement Systems (see above).

- To promote technical assistance, through the partners participating in the Working Group, in the submission of proposals to the Green Light Committee, and in the implementation of the project protocols.

- To re-assess, periodically, pilot projects whose applications are found to meet the requirements highlighted in the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*, including through site visits as WHO may deem necessary and appropriate.

Financing

Financing of the Working Group, including its subgroups, will be the responsibility of all participant member institutions. Travel expenses for participation in meetings of the Working Group will be shared between members, depending on the availability of funds. The travel expenses of participants from resource-limited countries should be funded by members from industrialized countries.

Meetings

Meetings of the Working Group will be held at least once every two years and will be convened by WHO in agreement with sponsoring members. Decisions will be taken by consensus. Meetings of subgroups will be held on an ad hoc basis when needed (based on recommendations of each subgroup and according to a priority scale).

ANNEX 4: LIST OF WHO REFERENCE DOCUMENTS FOR MDR-TB

Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance, Report No. 1. Geneva, Switzerland, 1997. WHO/TB/97.229.

Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance, Report No. 2. Geneva, Switzerland, 2000. WHO/TB/2000.278.

Basis for the Development of an Evidence-based Case-management Strategy for MDR-TB within the WHO's DOTS Strategy. Geneva, Switzerland, 1999. WHO/TB/99.260

Coordination of DOTS-Plus Pilot Projects for the Management of MDR-TB. Geneva, Switzerland, 1999. WHO/CDS/CPC/TB/99.262

DOTS-Plus and the Green Light Committee: Improving Access to Second-line Anti-TB Drugs. Geneva, Switzerland, 2000. WHO/CDS/TB/2000.283

Guidelines for Drug Susceptibility Testing for Second-line Anti-tuberculosis Drugs for DOTS-Plus. Geneva, Switzerland, 2001. WHO/CDS/TB/2001.288

Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of Multidrug-Resistant Tuberculosis (MDR-TB). Geneva, Switzerland, 2000. WHO/CDS/TB/2000.278

Guidelines for the Management of Drug-resistant Tuberculosis. Geneva, Switzerland, 1996. WHO/TB/96.210

Guidelines for Surveillance of Drug Resistance in Tuberculosis. Geneva, Switzerland, 1996. WHO/TB/96.216

Instructions for Applying to the Green Light Committee for Access to Second-line Anti-Tuberculosis Drugs. Geneva, Switzerland, 2001. WHO/CDS/TB/2001.286 (rev. 2)

Procurement of Second-line Anti-tuberculosis Drugs for DOTS-Plus Pilot Projects. Geneva, Switzerland, 2000. WHO/CDS/TB/2000.276

Progress in DOTS-Plus and the Management of Multidrug-resistant Tuberculosis. Geneva, Switzerland, 2001. WHO/CDS/TB/2001.292

Treatment of Tuberculosis: Guidelines for National Programmes. Geneva, Switzerland, 1997. WHO/TB/97.220 (rev.2)

ANNEX 5: STRUCTURE OF THE WORKING GROUP ON DOTS-PLUS FOR MDR-TB